CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040171

Trade Name : OXYCODONE AND ACETAMINBOPHEN TABLETS USP 5MG/325MG

Generic Name: Oxycodone and Acetaminophen Tablets USP 5mg and 325mg

Sponsor : Royce Laboratories, Inc.

Approval Date: October 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040171

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040171

APPROVAL LETTER

ANDA 40-171

OCT 30 1997

Royce Laboratories, Inc.
Attention: William Stahovec
16600 NW 54 Avenue
Miami, Florida 33014

Dear Sir:

This is in reference to your abbreviated new drug application dated November 14, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg.

Reference is also made to your amendments dated January 31 and September 9, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Oxycodone and Acetaminophen Tablets USP, 5 mg/325 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (PERCOCET® Tablets, 5 mg/325 mg of DuPont Merck Pharmaceutical Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 10/30/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040171

FINAL PRINTED LABELING

Each tablet contains:
Oxycodone hydrochloride, USP ..... 5 mg*
Acetaminophen, USP ..... 325 mg
*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone

Usual Adult Dosage:
For dosage and other prescribing information see accompanying product literature.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in a light, light-resistant container as defined by the USP.

DEA ORDER FORM REQUIRED

Royce™

NDC 51875-0403-2

OXYCODONE* AND ACETAMINOPHEN TABLETS, USP

CII

*WARNING: May be habit forming

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:

Exp. Date:

N 3 51875-0403-2 6

Each tablet contains:
Oxycodone hydrochloride, USP ..... 5 mg*
Acetaminophen, USP ..... 325 mg
*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone

Usual Adult Dosage:
For dosage and other prescribing information see accompanying product literature.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined by the USP.

DEA ORDER FORM REQUIRED

Royce™

NDC 51875-0403-4

OXYCODONE* AND ACETAMINOPHEN TABLETS, USP

CII

*WARNING: May be habit forming

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:

Exp. Date:

N 3 51875-0403-4 0

OXYCODONE* AND ACETAMINOPHEN TABLETS, USP

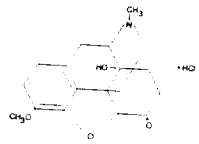
DESCRIPTION

Each tablet, for oral administration, contains:

Oxycodone hydrochloride (equivalent to 4.4815 mg of oxycodone)	5 mg
***WARNING: May be habit forming**	
Acetaminophen, USP	325 mg

In addition, each tablet also contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch and stearic acid.

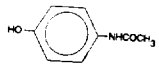
The oxycodone component is 14-hydroxydihydrocodeinone, a white, odorless, crystalline powder having a saline, bitter taste. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:



$C_{18}H_{21}NO_4.HCl$

Molecular Weight = 351.83

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder with a slightly bitter taste. It may be represented by the following structural formula:



$C_8H_9NO_2$

Molecular Weight = 151.17

CLINICAL PHARMACOLOGY

The principal ingredient, oxycodone, is a semisynthetic narcotic analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in this product are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic.

INDICATIONS AND USAGE

Oxycodone and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

Oxycodone and acetaminophen tablets should not be administered to patients who are hypersensitive to oxycodone or acetaminophen.

WARNINGS

Drug Dependence: Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of oxycodone and acetaminophen tablets, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, oxycodone and acetaminophen tablets are subject to the Federal Controlled Substances Act (Schedule II).

PRECAUTIONS

General

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of products containing oxycodone or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients: Oxycodone and acetaminophen should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients

Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using oxycodone and acetaminophen tablets should be cautioned accordingly.

Drug Interactions

Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with oxycodone and acetaminophen may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with narcotics may produce paralytic ileus.

Pregnancy

Teratogenic Effects: Pregnancy Category C: Animal reproductive studies have not been conducted with oxycodone and acetaminophen. It is also not known whether oxycodone and acetaminophen can cause fetal harm when administered to

a pregnant woman or can affect reproductive capacity. Oxycodone and acetaminophen should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects: Use of narcotics during pregnancy may produce physical dependence in the neonate.

Labor and Delivery: As with all narcotics, administration of oxycodone and acetaminophen to the mother shortly before delivery may result in some degree of respiratory depression in the newborn and the mother, especially if higher doses are used.

Nursing Mothers

It is not known whether oxycodone and acetaminophen are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxycodone and acetaminophen are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus. At higher doses, oxycodone has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

Oxycodone and acetaminophen tablets are a Schedule II controlled substance.

Oxycodone can produce drug dependence and has the potential for being abused. (See **WARNINGS**).

OVERDOSAGE

Acetaminophen

Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patient's estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural, or functional hepatic abnormalities.

Oxycodone

Signs and Symptoms: Serious overdosage with oxycodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of naloxone hydrochloride (usual initial adult dose 0.4 mg to 2 mg) should be administered preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation (see package insert). Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. Oxycodone and acetaminophen tablets are given orally. The usual adult dosage is one tablet every 6 hours as needed for pain.

HOW SUPPLIED

Oxycodone and acetaminophen tablets USP (5 mg oxycodone hydrochloride and 325 mg acetaminophen) are white, scored, round tablets debossed "403" above the score and "5-325" below the score on one side and with the Royce Logo on the other side. They are available as:

SIZE	ROYCE NDC NUMBER
Bottles of 100	51875-0403-1
Bottles of 500	51875-0403-2
Bottles of 1000	51875-0403-4

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Dispense in a tight, light-resistant container as defined by the USP.

DEA Order Form Required.

Caution - Federal law prohibits dispensing without prescription.

Royce Laboratories, Inc.
16600 NW 54 Avenue
Miami, FL 33014

Issued 8/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040171

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VII
Abbreviated New Drug Application Review

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 40-171

3. NAME AND ADDRESS OF APPLICANT
Royce Laboratories, Inc.
16600 NW 54 Avenue
Miami, Florida 33014

4. LEGAL BASIS for ANDA SUBMISSION
PERCOCET® Tablets, 5 mg/325 mg
DuPont Merck
Wilmington, Delaware 19880

All patents and exclusivities have expired for the drug substance, drug product and indications.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Oxycodone and Acetaminophen Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
11/14/95 Original Submission.
1/23/96 Correspondence - Response to request of 1/17/96.
1/31/97 Amendment - Response to Agency's letter of 5/29/96.
9/9/97 Amendment - Response to Agency's Facsimile of 8/29/97.

FDA:
1/17/96 Receipt acknowledged, request for container label comparison.
2/29/96 Issuance of Bioequivalence No Further Questions letter.
5/29/96 Issuance of Not Approvable letter.
8/29/97 Issuance of Facsimile Minor.

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesics

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

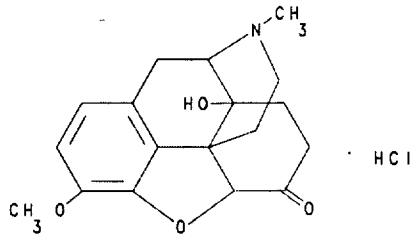
(b)4 - Confidential Business

13. DOSAGE FORM
Tablet for oral administration

14. POTENCY
5 mg/325 mg

15. CHEMICAL NAME AND STRUCTURE

Oxycodone Hydrochloride



Molecular Formula: $C_{18}H_{21}NO_4 \bullet HCl$

Molecular Weight: 351.83

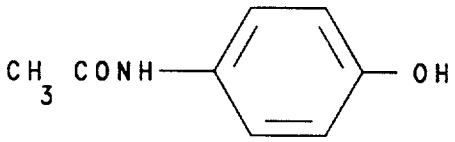
1. Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5α)-;

2. 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, hydrochloride.

3. 14-Hydroxydihydrocodeinone (Oxycodone component).

A white, odorless crystalline powder having a saline, bitter taste. It is derived from the opium alkaloid thebaine. Long rods from water, dec 270° - 272°C. $[\alpha]_D^{20}$ -125° (c = 2.5). One gram dissolves in 10 mL water. slightly soluble in alc.

Acetaminophen



Molecular Formula: $C_8H_9NO_2$
Molecular Weight: 151.17

1. Acetamide, N-(4-hydroxyphenyl)-;

2. 4'-Hydroxyacetanilide.

A white, odorless crystalline powder, possessing a slightly bitter taste. Large monoclinic prisms from water, mp 169 - 170.5°C. d_4^{21} 1.293. uv max (ethanol): 250 nm (ϵ 13,800). Very slightly sol in cold water, considerably more sol in hot water. Sol in methanol, ethanol, dimethylformamide, ethylene dichloride, acetone, ethyl acetate. Slightly sol in ether. Practically insol in petr ether, pentane, benzene. LD_{50} in mice (mg/kg): 338 orally, 500 i.p.

16. RECORDS AND REPORTS
2/27/96 - Review of Dissolution Data and a Waiver Request Division of Bioequivalence, L. Chuang.
4/12/96 - Chemistry review #1, G.J. Smith.
5/7/96 - Labeling review, A. Vezza.
5/6/97 - Labeling review, C. Hoppes.
8/14/97 - Chemistry reviw #2, G.J. Smith.

17. COMMENTS
The firm has resolved all major questions concerning the chemistry, manufacturing, and controls section of the application.

Labeling was found to be satisfactory.

Waiver request granted by the Division of Bioequivalence.

An acceptable EIR was issued by the Office of Compliance.

Methods Validation not required since drug substances and drug product are compendial.

The DMF's for the drug substances were satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
The application may be Approved.

19. REVIEWER: Glen Jon Smith

DATE COMPLETED: September 22, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040171

BIOEQUIVALENCE REVIEW(S)

ANDA 40-171

FEB 29 1996

Royce Laboratories Inc.
Attention: Loren Gelber Ph.D.
16600 NW 54th Avenue
Miami FL 33014

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Oxycodone and Acetaminophen Hydrochloride Tablets USP, 5 mg/325 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of 0.1 N hydrochloric acid at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than (b)(4) of the labeled amount of both acetaminophen and oxycodone is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FEB 27 1996

Acetaminophen and
Oxycodone HCl
Tablet, 325 mg/5 mg
ANDA # 40-171
Reviewer: L. Chuang

Royce Laboratories, Inc.
Miami, FL
Submission Date:
November 14,1995

Review of a Waiver Request

Oxycodone is a semisynthetic narcotic analgesic with multiple actions qualitatively similar to those of morphine. Its principal actions of therapeutic value in the drug product are analgesia and sedation. Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic.

The reference listed drug product is Percocet[R] tablet (acetaminophen/oxycodone HCl, 325 mg/5 mg) manufactured by Dupont Merck approved under NDA #85106 on 02/06/81.

The firm requests a waiver from the human *in vivo* bioequivalence testing requirements because acetaminophen/oxycodone HCl tablet, 325 mg/5 mg, is rated AA in *Approved Drug Products with Therapeutic Equivalence evaluation*, and the comparative dissolution testing data of the test and reference drug products conducted by the firm are presented below:

In Vitro Dissolution Testing

Drug (Generic Name): Acetaminophen/Oxycodone HCl
Dose Strength: 325 mg/5 mg
ANDA No.: 40-171
Firm: Royce Laboratories, Inc.

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 50
No. Units Tested: 12
Medium: 0.1 N Hydrochloric Acid Volume: 900 ml
Tolerance: NLT (b)(4) (Q) of both ingredients in 45 minutes (USP 23 & Royce)
Reference Drug: Percocet[R] Tablets (Dupont Merck)
Assay Methodology: (b)(4) - Confidential

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # MD-1199 Strength (mg): 325/5 Amount of Acetaminophen Dissolved	Reference Product Lot # EHL287A Strength (mg): 325/5 Amount of Acetaminophen Dissolved

	Mean %	Range	%CV	Mean %	Range	%CV
15	99.3	(b)4 - Confidential Business	1.3	66.1	(b)4 - Confidential Business	4.4
30	100.5		3.5	76.7		5.5
45	99.4		1.1	81.4		7.4
60	99.4		1.2	84.9		7.4
	Amount of Oxycodone Dissolved			Amount of Oxycodone Dissolved		
15	101.3	(b)4 - Confidential Business	1.1	97.7	(b)4 - Confidential Business	3.6
30	101.8		4.0	99.7		3.6
45	100.3		1.0	99.8		3.8
60	100.4		0.9	99.8		4.1

Content Uniformity N=10 (CV) = 100.5% (1.0%) for Acetaminophen in Test Drug
Content uniformity N=10 (CV) = 100.6% (1.2%) for Acetaminophen in Reference drug
Content Uniformity N=10 (CV) = 99.3% (0.9%) for Oxycodone in Test Drug
Content Uniformity N=10 (CV) = 99.5% (2.7%) for Oxycodone in Reference Drug

The formulation of the test drug product is presented below:

Ingredient	Amount per Tablet Test Product
Oxycodone Hydrochloride	5.0 mg
Acetaminophen	325.0 mg
Microcrystalline Cellulose	(b)4 - Confidential Business
Pregelatinized Starch	
Colloidal Silicon Dioxide	
Stearic Acid	
Magnesium Stearate	

Comment:

The test drug is in conventional dosage form and does not present bioequivalence problems. It also has met the proper *in vitro* dissolution standard that is acceptable to the specification published in USP 23. Therefore, a waiver from the human *in vivo* bioequivalence testing requirements is granted.

Recommendation:

1. The Division of Bioequivalence agrees that the information submitted by Royce Laboratories, Inc. demonstrates that Acetaminophen/Oxycodone HCl Tablet, 325 mg/5 mg, falls under 21 CFR Section 320.22 (c) of the

Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test tablet to be bioequivalent to Percocet[R] tablet, 325 mg/5 mg, manufactured by Dupont Merck.

2. The dissolution testing conducted by Royce Laboratories, Inc. on its Acetaminophen/Oxycodone HCl Tablet, 325 mg/5 mg, Lot #MD-1199, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 N hydrochloric acid at 37° C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than (b)4 - of the labeled amount of both acetaminophen and oxycodone is dissolved in 45 minutes.

(b)4 - Confidential Business

2/27/96

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

(b)4 - Confidential Business

2/27/96

cc: ANDA 40171 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Chuang), Drug File, Division File.

First Draft, LWC, 02/21/96, c:\wpfiles\40171w.n95
Pink Final, LWC, 02/27/96, x:\new\firmsnz\royce\ltrs&rev\40-71w.N95